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The effect of sodium-glucose cotransporter-2 inhibitors on inflammatory biomarkers: A meta-analysis of randomized controlled trials

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Abstract

Aims: To conduct a meta-analysis of randomized controlled trials (RCTs) to assess the effect of sodium-glucose cotransporter-2 (SGLT2) inhibitors on inflammatory biomarkers.

Methods: Medline, Embase and the Cochrane Library were searched for RCTs investigating the effect of SGLT2 inhibitors on inflammatory biomarkers, adipokine profiles and insulin sensitivity.

Results: Thirty-eight RCTs were included (14 967 participants, 63.3% male, mean age 62 ± 8.6 years) with a median (interquartile range) follow-up of 16 (12–24) weeks. Meta-analysis showed that SGLT2 inhibitors significantly improved adiponectin, interleukin-6, tumour necrosis factor receptor-1 (vs. placebo alone: standardized mean difference [SMD] 0.34 [95% confidence interval {CI} 0.23, 0.45], mean difference [MD] −0.85 pg/mL [95% CI −1.32, −0.38], SMD −0.13 [95% CI −0.20, −0.06], respectively), leptin and homeostatic model assessment of insulin resistance index (vs. control: SMD −0.20 [95% CI −0.33, −0.07], MD −0.83 [95% CI −1.32, −0.33], respectively). There were no significant changes in C-reactive protein (CRP), tumour necrosis factor-α, plasminogen activator inhibitor-1, fibroblast growth factor-21 or monocyte chemoattractant protein-1.

Conclusions: Our analysis shows that SGLT2 inhibitors likely improve adipokine biomarkers and insulin sensitivity, but there is little evidence that SGLT2 inhibitors improve other inflammatory biomarkers including CRP.

KEYWORDS

cardiovascular disease, dapagliflozin, empagliflozin, inflammation, mechanism of action, sodium-glucose co-transporter-2 inhibitors

1 | INTRODUCTION

In 2015, sodium-glucose cotransporter-2 (SGLT2) inhibitors were found to significantly reduce cardiovascular events in people with type 2 diabetes mellitus (T2DM) who are at the highest risk of experiencing such events.[1] When given to individuals with heart failure with reduced ejection fraction, SGLT2 inhibitors reduced cardiovascular mortality and hospitalizations for acute heart failure by approximately 25%[2,3] and in heart failure with preserved ejection fraction by approximately 20%.[4] Whilst SGLT2 inhibitors were initially designed as a medication for the treatment of T2DM, where they promote renal excretion of glucose, it remains unexplained how SGLT2 inhibitors exert their cardiorenal-protective effects. Multiple explanations for the underlying cardiovascular benefits have been described that extend beyond improved glycaemic control.[5] These include early natriuresis, reductions in plasma volume, improved vascular structure and function, renal collecting tubular extension, reduced blood pressure, modifications to tissue sodium handling, favouring of ketone body metabolism, reduced uric acid levels, reduced adipose tissue-mediated inflammation, reduced body mass and reduced oxidative stress.[5,6]

Of the mechanisms listed, inflammation is of particular interest as it has a significant role in the pathophysiology of T2DM,[7–9] and is increasingly recognized as a key player in the pathogenesis of cardiovascular disease (CVD).[10,11] Research from basic science models suggests that SGLT2 inhibitors may be anti-inflammatory. SGLT2 inhibitors may reduce tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1)[12] in apolipoprotein E knockout mice, IL-6 and tumour necrosis factor receptor-1 (TNFR1) in human proximal tubular cells,[13] and IL-6, TNF-α and MCP-1 in mouse models of diabetic kidney disease.[14] Furthermore, SGLT2 inhibitors may upregulate the production of adipokines in obese mice.[15] However, it remains uncertain whether these mechanisms apply to humans. Previous reviews have sought to understand whether inflammation plays a role in the cardiorenal-protective effects of SGLT2 inhibitors in humans, but none has been able to provide a quantitative, minimally biased assessment of the effect of SGLT2 inhibitors on biomarkers of inflammation.[16]

2 | METHODS

This review is written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Table S1) and registered with PROSPERO (CRD42022363880).[17]

2.1 | Search strategy

Medline, Embase and the Cochrane Library were searched from inception to January 2024 for trials investigating the use of SGLT2 inhibitors and measuring biomarkers of inflammation. The full search strategy can be found in Table S2. Medical subject heading (MeSH) terms were used where feasible. Following removal of duplicates, the results of the search were screened independently by three reviewers, before full-text eligibility assessment was performed independently by two reviewers (Figure 1).

2.2 | Study selection

Eligibility was restricted to prospective randomized controlled trials (RCTs), of either parallel or crossover design, that used SGLT2 inhibitors as intervention compared to any control other than different SGLT2 inhibitor drugs or doses. Observational studies, case reports and basic science reports without human participants were excluded. Adults were included if they were eligible for SGLT2 inhibitor prescription, including patients with T2DM, symptomatic chronic heart failure and chronic kidney disease. Trials were excluded if they included individuals with type 1 diabetes mellitus or paediatric participants. Trials of any study duration were included providing they reported the measurement of inflammatory biomarkers, regardless of the primary outcome measured. Trials were also excluded if they did not possess data that could be quantitatively analysed using meta-analysis.

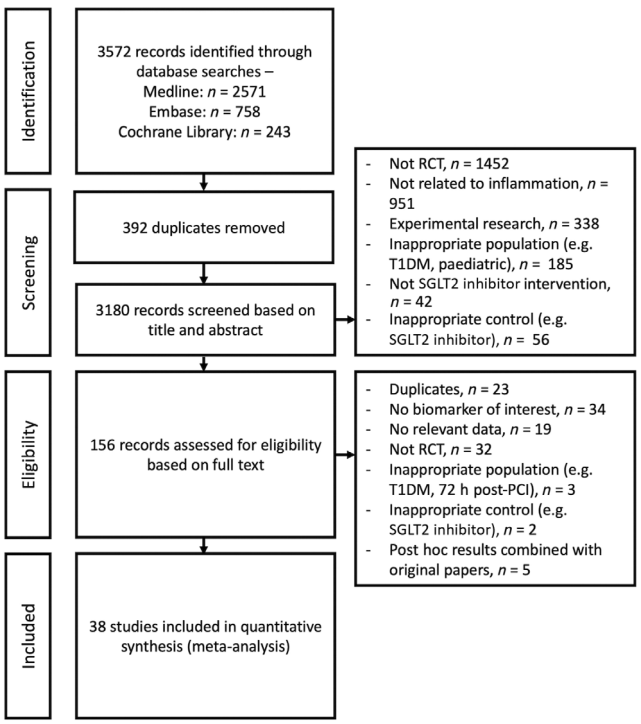


FIGURE 1 Flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines showing the method of identifying trials and reasons for exclusion. PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SGLT2, sodium-glucose cotransporter-2; T1DM, type 1 diabetes mellitus.

2.3 | Outcomes of interest and comparisons

The following biomarkers were selected a priori based on published evidence linking these biomarkers to inflammatory pathways. We specify where there were no data available to report a biomarker.

Inflammatory biomarkers—C-reactive protein (CRP), adiponectin, leptin, TNF-α, IL-6, TNFR1/2, plasminogen activator inhibitor-1 (PAI-1), fibroblast growth factor-21 (FGF21) and MCP-1.

Insulin sensitivity markers—homeostatic model assessment of insulin resistance index (HOMA-IR).

These biomarkers are established to be related to inflammation.[18–25] Of note, adiponectin is thought to increase IL-6.[26] Insulin resistance is a key promoter of chronic inflammation, therefore, HOMA-IR (a direct measure of insulin resistance) was included.[27]

Comparisons are made between study arms that were exposed to SGLT2 inhibitors compared with controls. Controls were defined as standard care including other glucose-lowering medications or placebo. Subgroup analysis was performed between comparisons made with placebo and other diabetes medications in an attempt to reduce heterogeneity.

2.4 | Data extraction and synthesis

Data were independently extracted into a preformatted Excel spreadsheet from eligible RCTs. Continuous outcomes for biomarkers were converted into equivalent, appropriate units. Where data were missing, these were sought via email from authors, and failing this, were considered missing at random. Furthermore, the following participant characteristics were extracted: age, sex, glycated haemoglobin (HbA1c), fasting plasma glucose, weight, body mass index (BMI), and diabetes duration. Data on the mean change in biomarkers of interest, alongside relevant standard deviations (SDs), and numbers of individuals in each relevant arm were collected.

2.5 | Associations of biomarker changes with clinically relevant outcomes

Where possible, clinically relevant outcomes were also collected such that analysis could be made for an association between changes in biomarkers with changes in clinically relevant outcomes. Analysis of a potential association with a particular biomarker would not be sought if there was no evidence of a change in this biomarker with SGLT2 inhibitors.

2.6 | Quality and risk of bias assessment

The Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess risk of bias.[28] The Grading of Recommendations Assessment, Development and Evaluation (GRADEpro) tool was used to assess outcome quality for each biomarker of interest.[29]

2.7 | Statistical analysis

Random-effects meta-analysis was used to assess the change in biomarkers with and without exposure to SGLT2 inhibitors in Stata (17.0, StataCorp LLC, College Station, TX, USA). Mean difference (MD) was used as default, unless different collection or measurement methodologies were used between trials for the same biomarker, in which case standardized mean difference (SMD) using Hedges' *G* was used.[30] Heterogeneity was quantified using the I^2 measure and the *p* value from the chi-squared test. I^2 > 50% was considered to represent moderate-to-high heterogeneity.[31] Small study effects were examined using funnel plots where the number of included trials was greater than 10, accompanied by Egger's regression test.[32] If the change in biomarker mean and SD were not available, the SD was calculated from the standard error of the mean, or values were estimated using methodology from the Cochrane handbook.[33] In cases where the median and interquartile range were provided in place of mean and SD, the mean and SD were estimated using methodology described by Wan et al.[34] In a minority of cases, if the SD was missing and could not be estimated, data were sought from the authors and failing this, values were imputed using the validated methodology described by Ma et al.[35] Descriptive statistics are reported as means ± SD. Baseline characteristic averages were calculated as the mean for each trial, weighted by the number of participants in the trial.

3 | RESULTS

Of the 38 RCTs used in this analysis, 35 were parallel trials and three were of crossover design.[36–38] All trials were prospective, and data were obtained from post hoc analyses in four trials[37–40] and partly obtained in three trials.[13,41–44] In total, 8589 included participants were treated with SGLT2 inhibitors, with a mean age of all participants of 62.0 ± 8.6 years, 63.3% were male and the median (interquartile range) follow-up was 16 (12–24) weeks (Table 1). The trials were performed in 13 different countries (17 from Japan,[40,47,55–57,59,64–67,69–75] three from the United Kingdom,[48,52,60] two from Denmark,[36,39] two from Germany,[37,54] two from the Netherlands,[38,53] two from Thailand,[50,62] two from the United States,[68,76] one from Austria,[46] one from Brazil,[51] one from China,[45] one from Finland,[61] one from Malaysia[58] and one from Sweden[63]) and two were multinational.[49,77] Participants had a mean HbA1c of 64.7 ± 9.6 mmol/mol, a mean BMI of 30.9 ± 5.4 kg/m^2 and a mean diabetes duration of 11.9 ± 7.2 years (Table 1). Most trials used either dapagliflozin or empagliflozin (dapagliflozin 16 trials, empagliflozin nine trials, ipragliflozin six trials, canagliflozin two trials, luseogliflozin two trials, tofogliflozin two trials and empagliflozin with licogliflozin one trial). For the dapagliflozin and empagliflozin trials, all used licensed doses, with the majority of dapagliflozin trials using 10 mg and empagliflozin trials using 25 mg. SGLT2 inhibitors were compared against placebo in 25 trials, specific glucose-lowering medications (glibenclamide, glimepiride, pioglitazone, pioglitazone with glimepiride, metformin in two trials, sitagliptin, vildagliptin and voglibose) in nine trials and standard care in four trials.

TABLE 1 Baseline characteristics of the included 38 trials.

Study name and year	No. included	Duration, weeks	Country	Study arms	Primary outcomes	Age, years ± SD	Sex, % male	HbA1c, mmol/mol OR % ± SD	FPG, mg/dL ± SD	BMI, kg/m^2 ± SD	Diabetes duration, years ± SD
Diao 2023[45]	46	24	China	Dapagliflozin Placebo	Cardiac function index	65.9 ± 9.8	43.5	8.4 ± 0.6	146.5 ± 15.3	26.9 ± 3.1	-
Antlanger 2022[46]	45	12	Austria	Empagliflozin Placebo	Serum angiotensin-(1–7)	64.1 ± 11.8	69.0	6.2 ± 0.8	126.3 ± 46.7	28.2 ± 3.8	-
Ejiri 2022[47]	157	12	Japan	Luseogliflozin Voglibose	Brain natriuretic peptide	73.3 ± 7.7	63.1	7.0 ± 0.7	-	25.3 ± 4.3	6.6 ± 6.4
Omar 2022[39]	190	12	Denmark	Empagliflozin Placebo	Growth differentiation factor-15, troponin T, CRP	64.0 ± 11.0	85.0	39.3 ± 4.8	-	29.0 ± 4.8	-
Sargeant 2022[48]	34	24	UK	Empagliflozin Placebo	Postprandial circulating total peptide-YY	62.3 ± 8.9	61.8	52.0 ± 5.2	121.2 ± 24.7	32.5 ± 4.3	6.8 ± 3.7
Suhrs 2022[36]	19	12	Denmark	Empagliflozin Placebo	Coronary flow velocity reserve	-	63.0	76.3 ± 16.1	-	30.5 ± 6.1	11.6 ± 8.1
Oldgren 2021[49]	49	6	Multiple countries	Dapagliflozin Placebo	Left atria and ventricle function, mass and volumes; myocardial metabolism	64.4 ± 7.2	53.1	6.7 ± 0.6	137.6 ± 19.7	30.2 ± 3.7	4.5 ± –
Phrueksotsai 2021[50]	38	12	Thailand	Dapagliflozin Placebo	Intrahepatic lipid content	59.2 ± 7.3	31.6	8.0 ± 0.7	147.9 ± 31.2	29.2 ± 4.0	5.7 ± 5.9
Sposito 2021[51]	97	12	Brazil	Dapagliflozin Glibenclamide	Rest and post-ischaemic/ reperfusion FMD	57.5 ± 7.0	60.5	7.9 ± 0.9	174.0 ± 50.1	30.5 ± 4.5	9.5 ± 7.0
Brown 2020[52]	66	52	Scotland	Dapagliflozin Placebo	Left ventricle mass	65.5 ± 6.9	57.6	60.9 ± 10.6	144.9 ± 53.3	32.5 ± 4.4	10.3 ± 6.7
de Boer 2020[53]	124	12	Netherlands	Licogliflozin + empagliflozin Placebo	Brain natriuretic peptide	68.0 ± 9.2	71.8	-	-	32.1 ± 5.2	-
Kahl 2020[54]	84	24	Germany	Empagliflozin Placebo	Liver fat content	62.1 ± 8.5	69.0	50.5 ± 7.0	132.3 ± 24.3	32.3 ± 4.4	3.2 ± 2.3
Katakami 2020[55]	339	104	Japan	Tofogliflozin Standard care	Mean and maximum common carotid intima-media thickness	61.1 ± 9.5	58.4	57.0 ± 7.9	140.4 ± 31.5	27.0 ± 5.2	12.3 ± 8.3
Kinoshita 2020[56]	98	28	Japan	Dapagliflozin Pioglitazone + glimepiride	Liver-to-spleen ratio	59.0 ± 1.0	45.9	57.9 ± 1.0	143.0 ± 3.3	28.8 ± 0.5	7.2 ± 0.5
Sakurai 2020[57]	49	12	Japan	Empagliflozin Standard care	Plasminogen activator inhibitor-1 and fibrinolytic activity	58.6 ± 12.6	57.1	7.9 ± 0.7	163.2 ± 43.7	27.6 ± 6.0	-
Sato 2020[40]	35	26	Japan	Dapagliflozin Standard care	Epicardial adipose tissue volume	67.5 ± 6.0	77.1	7.2 ± 0.8	140.7 ± 31.3	25.7 ± 4.1	-
Zainordin 2020[58]	72	12	Malaysia	Dapagliflozin Placebo	FMD and nitroglycerin-mediated dilatation	57.6 ± 7.9	76.4	9.5 ± 1.7	182.4 ± 77.2	28.7 ± 4.2	9.8 ± 6.6

TABLE 1 (Continued)

Study name and year	No. included	Duration, weeks	Country	Study arms	Primary outcomes	Age, years ± SD	Sex, % male	HbA1c, mmol/mol OR % ± SD	FPG, mg/dL ± SD	BMI, kg/m^2 ± SD	Diabetes duration, years ± SD
Aso 2019[59]	57	24	Japan	Dapagliflozin Standard care	Soluble dipeptidyl peptidase-4 and liver function	56.6 ± 12.5	59.7	8.1 ± 1.4	137.3 ± 48.6	27.9 ± 4.2	-
Bosch 2019[37]	58	6	Germany	Empagliflozin Placebo	Determinants for improvement in arterial stiffness	62.0 ± 7.0	59.0	50 ± 8.7	136.5 ± 31.4	29.5 ± 3.9	-
Javed 2019[60]	39	12	UK	Empagliflozin Metformin	Anthropometric and body composition parameters	-	-	-	-	37.9 ± 7.0	-
Latva-Rasku 2019[61]	31	8	Finland	Dapagliflozin Placebo	Insulin sensitivity	61.0 ± 7.9	80.6	52.0 ± 6.5	163.6 ± 32.3	31.9 ± 4.5	7.5 ± 3.7
Phrommintikul 2019[62]	49	26	Thailand	Dapagliflozin Vildagliptin	Haemodynamic, metabolic and inflammatory biomarkers	63.2 ± 7.9	53.1	8.2 ± 1.3	143.5 ± 35.2	25.3 ± 3.1	-
Dekkers 2018[38]	31	12	Netherlands	Dapagliflozin Placebo	24-h urinary albumin excretion rate	62.0 ± 8.1	77.4	56.0 ± 8.5	-	31.0 ± 5.4	-
Eriksson 2018[63]	42	12	Sweden	Dapagliflozin Placebo	Liver fat content	65.3 ± 6.3	78.6	57.3 ± 7.6	165.5 ± 31.5	30.4 ± 3.0	6.6 ± 5.1
Hattori 2018[64]	102	52	Japan	Empagliflozin Placebo	Insulin resistance and CRP	57.8 ± 11.1	77.5	6.9 ± 1.0	134.7 ± 30.9	30.5 ± 4.6	-
Seino 2018[65]	233	16	Japan	Luseogliflozin Placebo	HbA1c, plasma glucose, glucagon, C-peptide immunoreactivity, glycosylated albumin, weight, and waist circumference	57.3 ± 10.5	69.9	8.7 ± 0.8	168.0 ± 40.8	25.3 ± 3.5	11.8 ± 7.3
Hayashi 2017[66]	80	12	Japan	Dapagliflozin Sitagliptin	Low-density lipoprotein and high-density lipoprotein cholesterol	54.0 ± 8.5	77.5	7.6 ± 1.4	145.4 ± 52.9	28.0 ± 3.8	8.3 ± 5.4
Ito 2017[67]	66	24	Japan	Ipragliflozin Pioglitazone	Liver-to-spleen ratio	58.2 ± 10.9	48.6	8.4 ± 1.4	164.9 ± 45.0	30.3 ± 5.6	9.1 ± 5.8
Neal 2017[68]	10 142	188.2	USA	Canagliflozin Placebo	Death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke	63.3 ± 8.3	64.2	8.2 ± 0.9	-	32.0 ± 5.9	13.5 ± 7.8
Shigiyama 2017[69]	74	16	Japan	Dapagliflozin Metformin	FMD	59.6 ± 9.2	63.6	50.9 ± 5.6	136.6 ± 23.7	26.6 ± 4.0	5.9 ± 4.3
Ishihara 2016[70]	255	16	Japan	Ipragliflozin Placebo	HbA1c	58.9 ± 10.5	61.2	71.1 ± 8.8	160.1 ± 44.9	25.9 ± 3.6	13.2 ± 8.0

(Continues)

TABLE 1 (Continued)

Study name and year	No. included	Duration, weeks	Country	Study arms	Primary outcomes	Age, years ± SD	Sex, % male	HbA1c, mmol/mol OR % ± SD	FPG, mg/dL ± SD	BMI, kg/m^2 ± SD	Diabetes duration, years ± SD
Kashiwagi 2015 (CL0105)[71]	129	16	Japan	Ipragliflozin Placebo	HbA1c	59.4 ± 10.0	69.7	8.3 ± 0.8	175.0 ± 40.8	25.5 ± 3.5	6.7 ± 6.0
Kashiwagi 2015 (CL0106)[72]	168	24	Japan	Ipragliflozin Placebo	HbA1c	56.7 ± 10.2	58.9	8.3 ± 0.7	165.9 ± 28.2	25.8 ± 4.0	7.7 ± 5.5
Kashiwagi 2015 (CL0107)[73]	151	24	Japan	Ipragliflozin Placebo	HbA1c	56.2 ± 10.8	74.2	8.3 ± 0.7	171.9 ± 34.1	27.1 ± 4.0	6.8 ± 4.9
Kashiwagi 2015 (CL0109)[74]	240	24	Japan	Ipragliflozin Placebo	HbA1c	59.7 ± 9.6	65.9	8.4 ± 0.7	178.5 ± 33.3	25.3 ± 3.4	10.5 ± 6.8
Kaku 2014[75]	229	24	Japan	Tofogliflozin Placebo	HbA1c	57.2 ± 9.7	66.8	8.4 ± 0.8	168.9 ± 31.0	25.5 ± 4.1	6.4 ± 5.9
Cefalu 2013[76]	967	52	USA	Canagliflozin Glimepiride	HbA1c	56.0 ± 9.1	52.5	7.8 ± 0.8	164.7 ± 36.9	31.1 ± 5.5	6.7 ± 5.3
Bailey 2012[77]	282	24	Multiple countries	Dapagliflozin Placebo	HbA1c	53.0 ± 10.5	50.0	7.9 ± 1.1	158.3 ± 34.0	31.8 ± 5.4	1.4 ± 2.5

Note: Values given as mean ± SD. Values rounded to one decimal place. '-' denotes data unavailable. HbA1c units represent those found in each paper. See results section for average HbA1c.
Abbreviations: BMI, body mass index; CRP, C-reactive protein; FMD, flow-mediated dilatation; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; SD, standard deviation.

3.1 | Risk of bias and evidence quality

Half of the outcomes provided moderate- or high-certainty evidence (Table S3). The RoB 2 tool was used to assess the randomized trials for risk of bias. Of the 38 trials, 17 were deemed to have 'low' risk of bias,[36,37,39,46–48,52,54,55,61,63,68–70,75–77] 14 warranted 'some concern'[38,40,49–51,56–58,60,65,67,71,73,74] and seven were judged as having a 'high' risk of bias[45,53,59,62,64,66,72] (Table S4). The biomarkers included in high-risk trials included CRP (4/16), adiponectin (4/20), leptin (2/12), HOMA-IR (4/13) and TNF-α (3/5). Concerns regarding the randomization process were present for 36.8% of the trials. Risk of bias in assignment to intervention was the principal reason resulting in seven trials being considered as having a high risk of bias.

3.2 | Inflammatory biomarkers

3.2.1 | C-reactive protein

From the analysis of 16 trials and 1435 participants at follow-up, use of SGLT2 inhibitors was associated with no significant MD in CRP levels compared to control (MD −0.10 mg/L, 95% confidence interval [CI] −0.35, 0.15). There was also no significant difference between groups in subgroup analysis. Overall heterogeneity was high ($I^2 = 81.0\%$, $p < 0.1$) and remained moderate in the placebo subgroup ($I^2 = 61.1\%$, $p < 0.1$) and high in the diabetes medications subgroup ($I^2 = 93.0\%$, $p < 0.1$; Figure 2A).

3.2.2 | Fibroblast growth factor-21

From the analysis of four trials and 157 participants at follow-up, use of SGLT2 inhibitors was associated with no significant SMD in FGF21 levels versus placebo (SMD −0.17 [95% CI −0.47, 0.14]). There were no included trials using diabetes medications as control (Figure 2B).

3.2.3 | Monocyte chemoattractant protein-1

From the analysis of three trials and 291 participants at follow-up, use of SGLT2 inhibitors was associated with no significant SMD in MCP-1 levels compared to control (SMD −0.07 [95% CI −0.29, 0.16]). There was no significant difference between groups in subgroup analysis (Figure 2C).

3.3 | Inflammatory biomarkers—Adipokines

3.3.1 | Adiponectin

From the analysis of 20 trials and 2789 participants at follow-up, use of SGLT2 inhibitors was associated with no significant SMD in adiponectin levels compared to control (SMD −0.24 [95% CI −1.01, 0.53]). In subgroup analysis, adiponectin was significantly increased versus

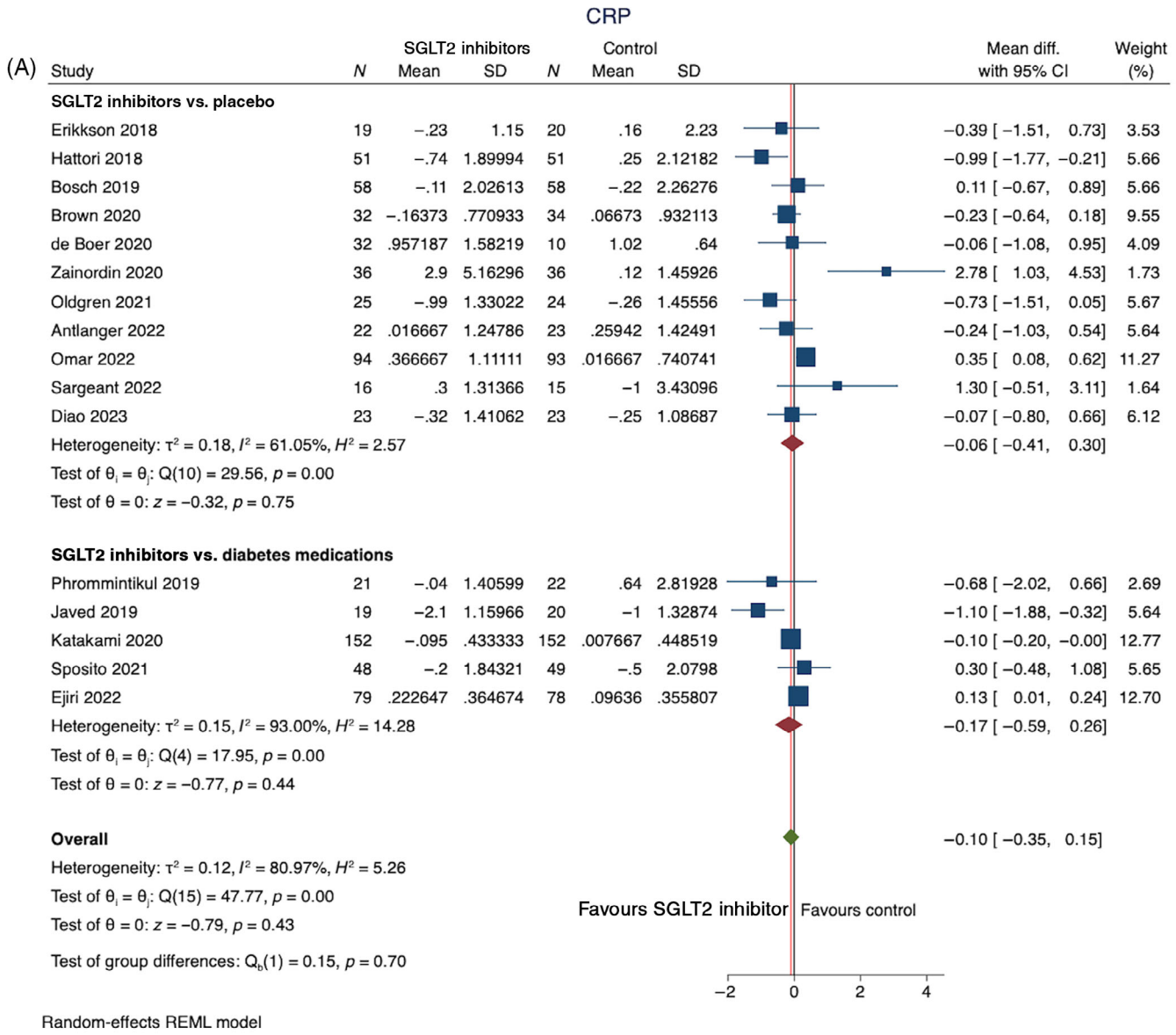


FIGURE 2 Forest plots showing the outcomes for sodium-glucose cotransporter-2 (SGLT2) inhibitor versus control groups for inflammatory biomarkers: (A) C-reactive protein (CRP) as mean difference. CRP levels reported as mg/L. (B) Fibroblast growth factor-21 (FGF21) as standardized mean difference (Hedges' G). (C) Monocyte chemoattractant protein-1 (MCP-1) as standardized mean difference (Hedges' G).

placebo (SMD 0.34 [95% CI 0.23, 0.45]) with no difference versus diabetes medications. Overall heterogeneity was high ($I^2 = 98.9\%$, $p < 0.1$), in the placebo subgroup it was low, and in the diabetes medications subgroup it was high ($I^2 = 99.3\%$, $p < 0.1$; Figure 3A).

3.3.2 | Leptin

From the analysis of 12 trials and 1509 participants at follow-up, use of SGLT2 inhibitors was associated with a significant standardized mean reduction in leptin compared to control (SMD −0.20 [95% CI −0.33, −0.07]). In subgroup analysis, leptin was significantly reduced versus placebo (SMD −0.21 [95% CI −0.36, −0.07]) with no difference versus diabetes medications. Overall heterogeneity was low (Figure 3B).

3.3.3 | Tumour necrosis factor-alpha

From the analysis of five trials and 259 participants at follow-up, use of SGLT2 inhibitors was associated with no significant SMD in TNF-α levels compared to control (SMD −0.30 [95% CI −0.67, 0.08]). There was no significant difference between groups in subgroup analysis. Overall heterogeneity was moderate ($I^2 = 55.4\%$, $p < 0.1$) and not fully explained by subgroup analysis (Figure 3C).

3.3.4 | Interleukin-6

From the analysis of four trials and 228 participants at follow-up, use of SGLT2 inhibitors was associated with no significant mean difference in IL-6 levels compared to control (MD −0.34 pg/mL

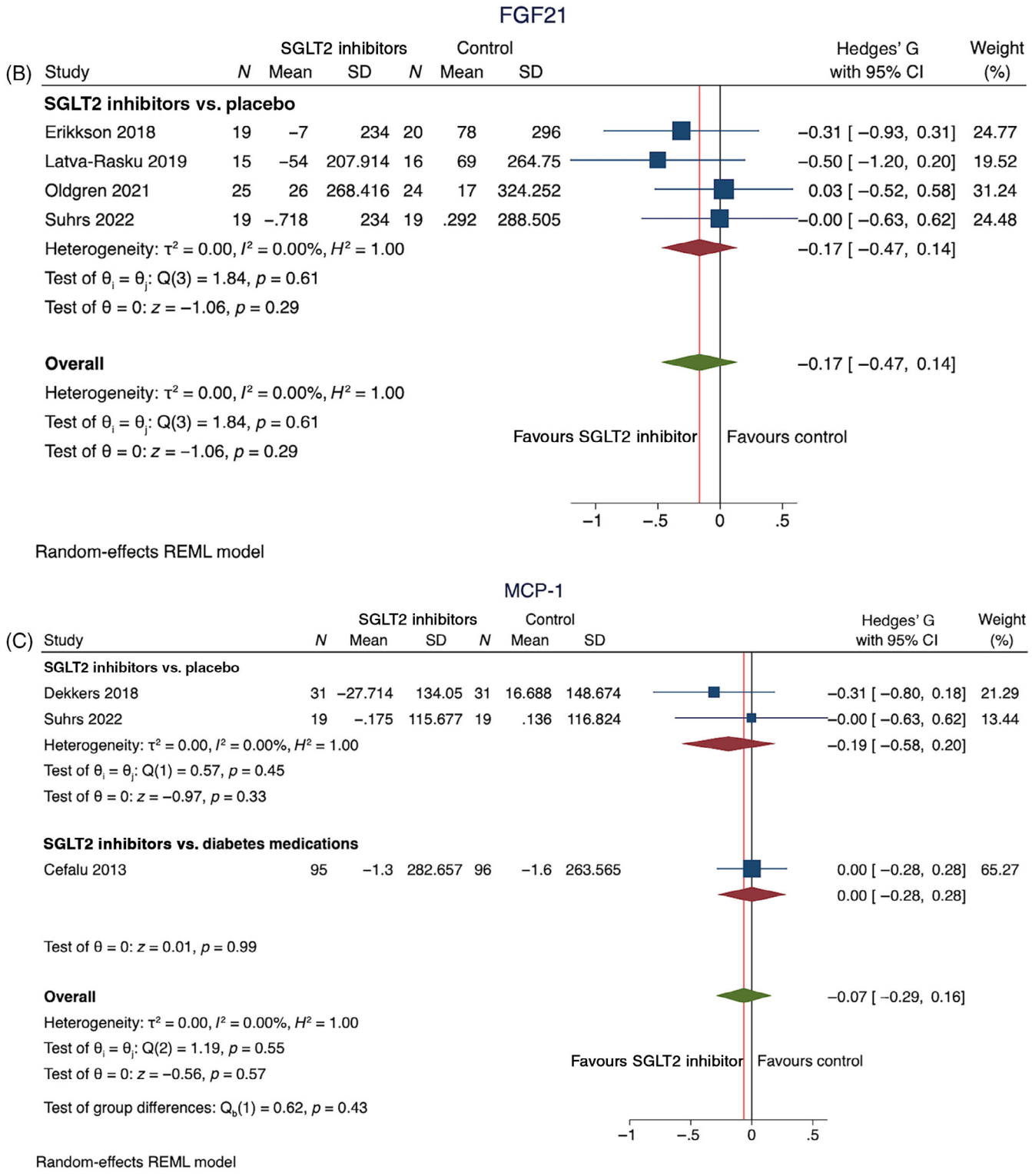


FIGURE 2 (Continued)

[95% CI −1.40, 0.72]). In subgroup analysis, IL-6 was significantly reduced versus placebo (MD −0.85 pg/mL [95% CI −1.32, −0.38]) and significantly increased versus diabetes medications (MD 1.20 pg/mL [95% CI 0.41, 1.99]). Overall heterogeneity was high ($I^2 = 86.0\%$, $p < 0.1$), but explained by subgroup analysis (Figure 3D).

3.3.5 | Plasminogen activator inhibitor-1

From the analysis of three trials and 277 participants at follow-up, use of SGLT2 inhibitors was associated with no significant SMD in PAI-1 levels compared to control (SMD −0.07 [95% CI −0.30, 0.17]). There was no significant difference between groups in subgroup analysis (Figure 3E).

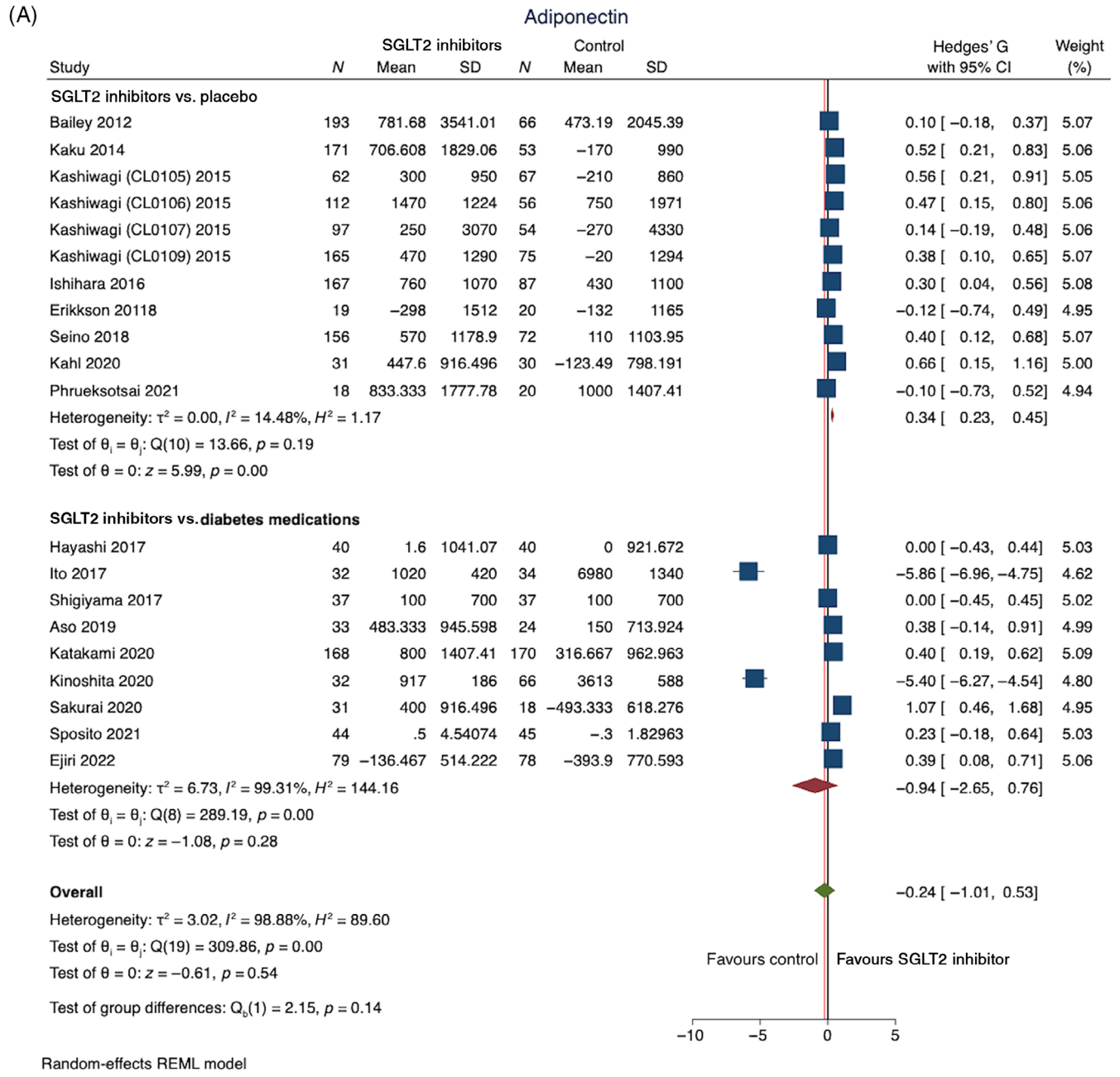


FIGURE 3 Forest plots showing the outcomes for sodium-glucose cotransporter-2 (SGLT2) inhibitor versus control groups for inflammatory biomarkers—adipokines: (A) Adiponectin as standardized mean difference (Hedges' G). (B) Leptin as standardized mean difference (Hedges' G). (C) Tumour necrosis factor-alpha (TNF-α) as standardized mean difference (Hedges' G). (D) Interleukin-6 (IL-6) as mean difference. IL-6 levels reported as pg/mL. (E) Plasminogen activator inhibitor-1 (PAI-1) as standardized mean difference (Hedges' G). (F) Tumour necrosis factor receptor-1 (TNFR1) as standardized mean difference (Hedges' G).

3.3.6 | Tumour necrosis factor receptor-1

From the analysis of two trials and 3561 participants at follow-up, use of SGLT2 inhibitors was associated with a significant standardized mean reduction in TNFR1 levels versus placebo (SMD −0.13 [95% CI −0.20, −0.06]). There were no included trials using diabetes medications as control (Figure 3F).

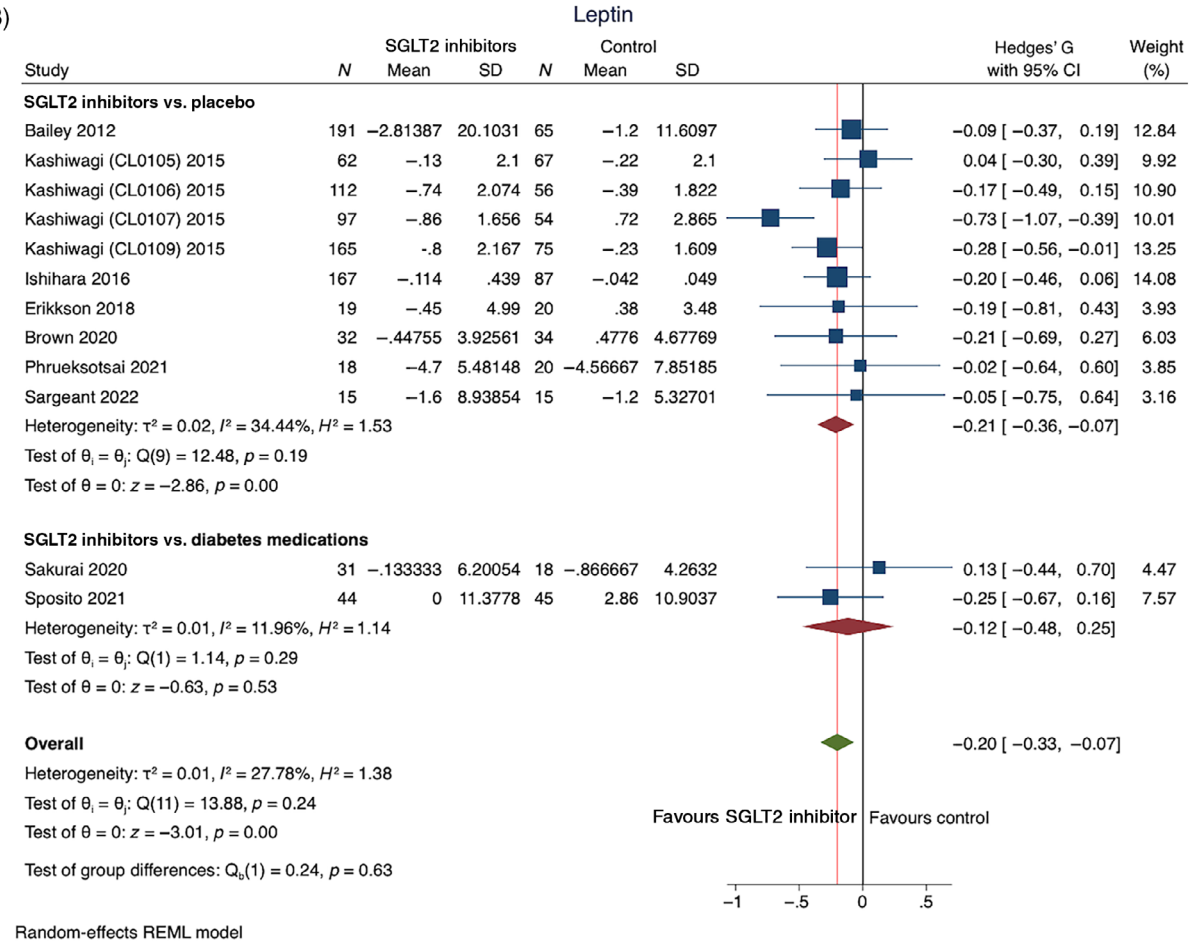
There were not enough data available in the literature to analyse TNFR2.

3.4 | Insulin sensitivity markers

3.4.1 | Homeostatic model assessment of insulin resistance

From the analysis of 13 trials and 1066 participants at follow-up, use of SGLT2 inhibitors was associated with a significant mean reduction in HOMA-IR compared to control (MD −0.83 [95% CI −1.32, −0.33]). In subgroup analysis, HOMA-IR was significantly reduced versus placebo

(B)



(C)

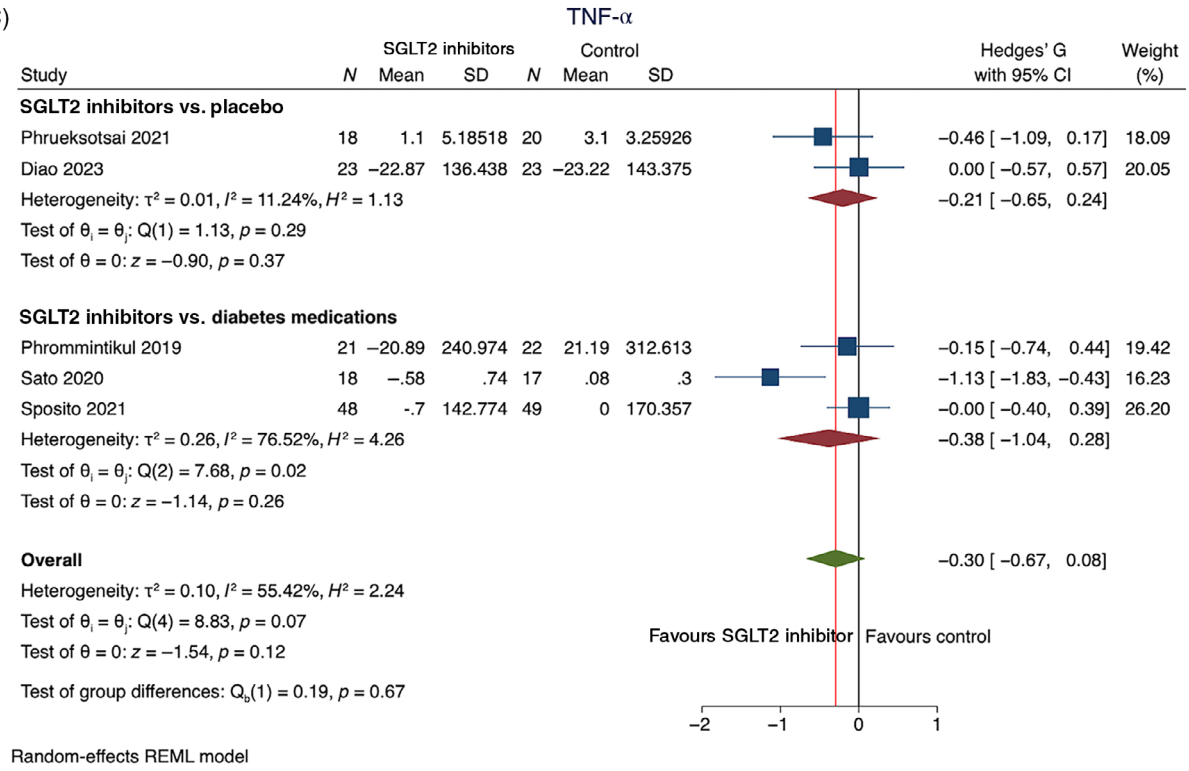


FIGURE 3 (Continued)

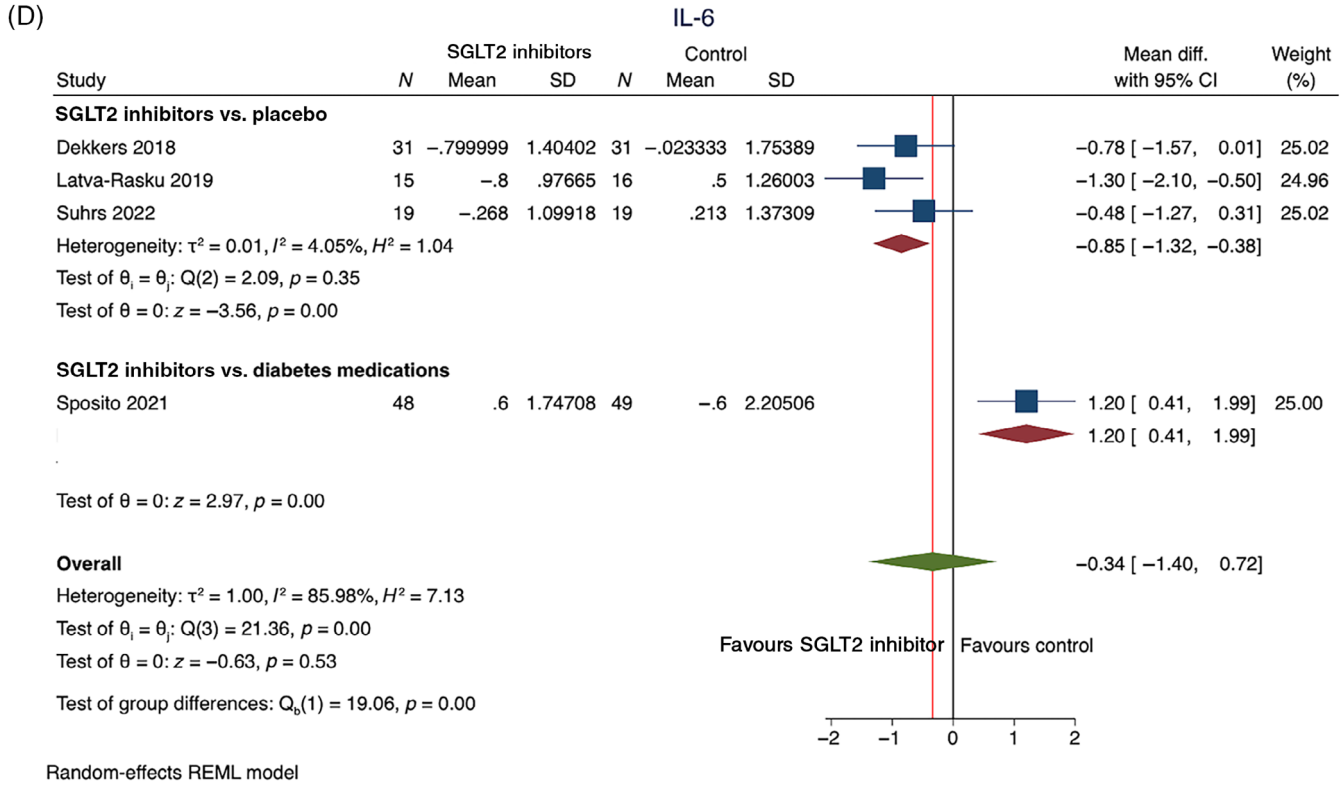


FIGURE 3 (Continued)

(MD −1.35 [95% CI −1.97, −0.74]) with no difference versus diabetes medications. Overall heterogeneity was high ($I^2 = 87.3\%$, $p < 0.1$) and not explained by subgroup analysis with placebo ($I^2 = 67.9\%$, $p < 0.1$) or diabetes medication subgroups ($I^2 = 85.9\%$, $p < 0.1$; Figure 4).

3.5 | Clinically relevant outcomes

There were insufficient data available on clinically relevant outcomes.

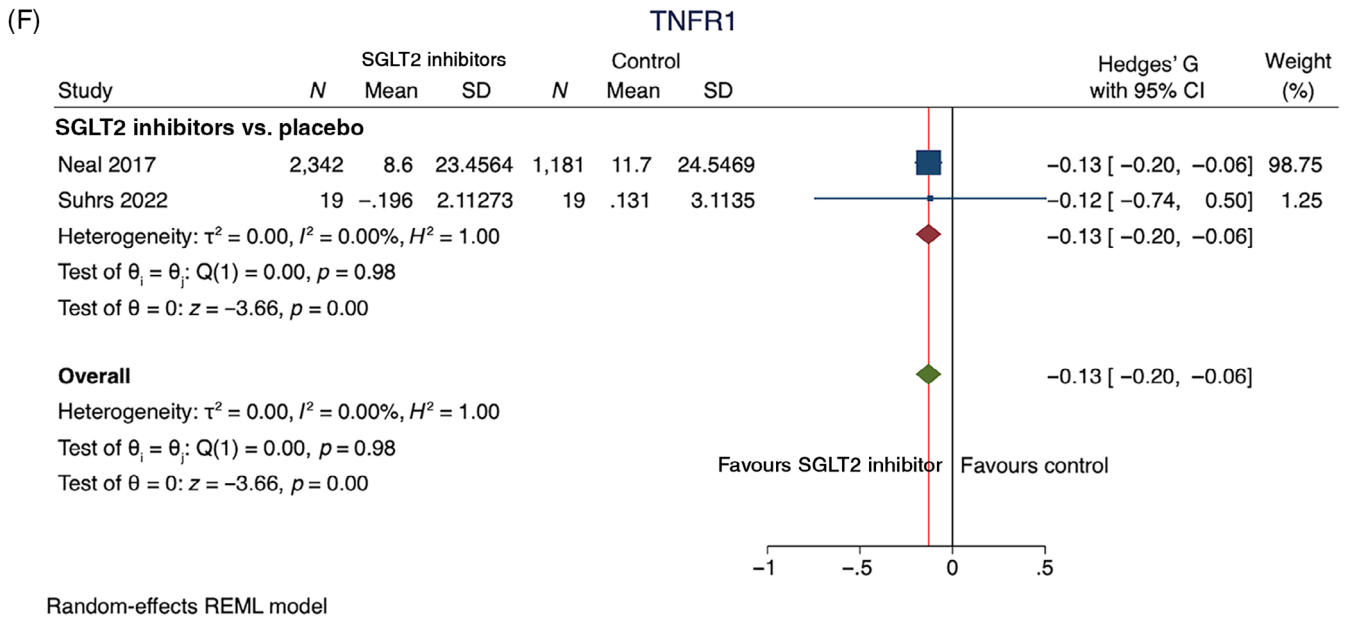


FIGURE 3 (Continued)

3.6 | Sensitivity analyses

Sensitivity analyses were conducted investigating the effect of using MD and SMD for each biomarker (Table S5) as well as the effect of stratifying papers by their risk of bias (Table S6). Visual assessment of funnel plots and Egger's regression test showed there was no evidence of small study effects in any of the outcomes (Figure S1–S4).

4 | DISCUSSION

This is the largest review to date encompassing randomized data that provides Cochrane-standard mitigation of bias, showing that SGLT2 inhibitors likely improve adipokine profiles and insulin sensitivity. However, in this analysis, SGLT2 inhibitors did not appear to improve other biomarkers of inflammation when compared to placebo and other glucose-lowering medications. Our results demonstrate that SGLT2 inhibitors significantly improved adiponectin, IL-6 and TNFR1 versus placebo, as well as leptin and HOMA-IR versus control. The reduction in HOMA-IR may be secondary to improved glucose handling as SGLT2 inhibitors are known to increase renal glucose excretion and reduce insulin secretion.[78] TNFR1 was found to be reduced by SGLT2 inhibitors, but this result should be viewed with caution as it was obtained from the analysis of only two trials.

Obesity is a risk factor for CVD; adipocytes produce immunomodulatory factors that are thought to mediate this link.[79] This review shows that SGLT2 inhibitors improve adiponectin and IL-6 versus placebo, and leptin versus control. These results support the hypothesis that SGLT2 inhibitors improve adipokine biomarkers. It is plausible that this could be a contributory mechanism by which SGLT2 inhibitors exert their cardiovascular-protective effects. Nevertheless, contrary to our initial hypothesis, this meta-analysis shows that there is little evidence to support the hypothesis that SGLT2 inhibitors improve inflammatory biomarkers, other than adipokines. This adds weight to the following assertion, but does not prove, that the cardioprotective mechanisms of SGLT2 inhibitors may not be due to an anti-inflammatory mechanism. This is in contrast to our previous publication showing that glucagon-like peptide-1 receptor agonists, which also have cardiorenal-protective effects, improve biomarkers of inflammation including CRP and TNF-α.[80] Trials have shown that SGLT2 inhibitors have effects beyond improving glucose levels by normalizing blood pressure, lowering weight/visceral adiposity, improving arterial stiffness and reducing uric acid concentrations.[81–83] As mentioned in the introduction, there is evidence from animal studies that suggests SGLT2 inhibitors may be anti-inflammatory. This highlights a need for further research, to better understand the difference in the effect of SGLT2 inhibitors in animal models compared to humans.

Our finding that SGLT2 inhibitors significantly affect adipocyte sensitivity profiles is supported by Wang et al.,[84] who also reported that, when compared to placebo, adiponectin is significantly raised, and both leptin and PAI-1 levels are significantly reduced. However, the authors conclude that SGLT2 inhibitors are anti-inflammatory, particularly reporting a significant reduction in CRP when compared to placebo. We included additional trials comparing CRP to placebo and it is suspected that Wang et al. may have used median change, as opposed to mean change, or inappropriately converted units when reporting CRP outcomes. Additionally, they reported data from Seino 2018[65] as CRP when the paper investigated C-peptide immunoreactivity (CPR) instead, as well as reporting data from Hao 2022[85] which was not a randomized trial. This may further explain the finding of a significant reduction in CRP compared to placebo reported by Wang

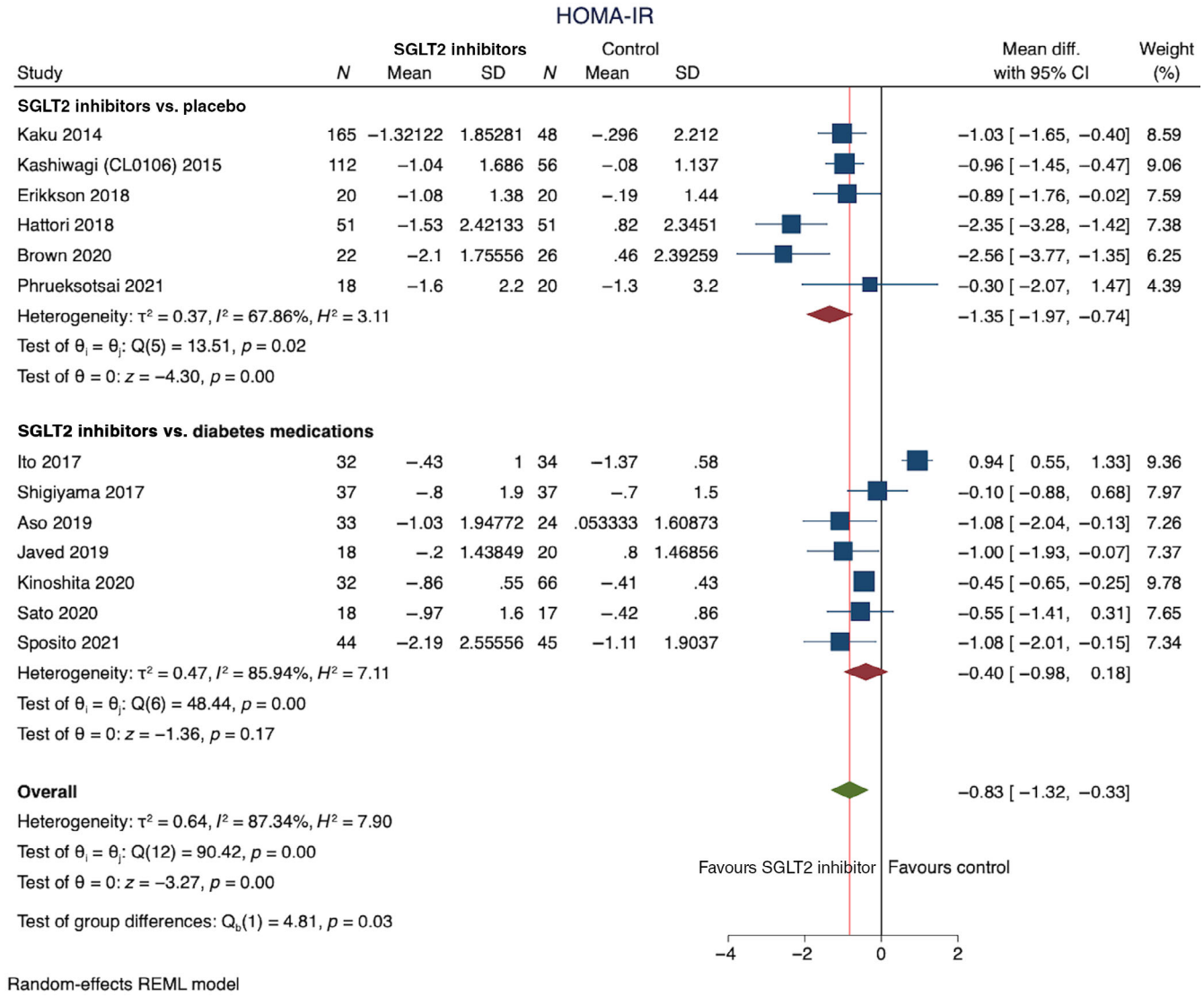


FIGURE 4 Forest plot showing the outcome for sodium-glucose cotransporter-2 (SGLT2) inhibitor versus control groups for the insulin sensitivity marker, homeostatic model assessment for insulin resistance (HOMA-IR) as mean difference.

et al.[84] Despite this difference, the data from Wang et al. support the hypothesis that SGLT2 inhibitors do not have an anti-inflammatory action, but instead alter adipokine profiles as they report SGLT2 inhibitors do not significantly reduce any inflammatory biomarker when compared to other glucose-lowering medications other than the adipokine leptin.

In terms of limitations, it was necessary to include many trials as all trials on this topic are small. Most trials investigating SGLT2 inhibitors include inflammatory biomarkers as secondary outcomes, often in supplements, occasionally with errors in units. In four cases, biomarker data were only found in post hoc analyses. Despite the evidence base being heterogenous and carrying some risk of bias, this analysis was an effective way to answer our study question using currently published data and, in order to address heterogeneity, subgroup and sensitivity analyses were performed. This analysis would be surpassed by a dedicated clinical trial, although the number of participants required may prohibit such a study design in this context. Where possible, missing data were estimated or imputed (using validated Cochrane-endorsed methods), but in a minority of cases, trials had to be excluded. Follow-up was also short in many trials. Extensive exclusion criteria were often employed in the included RCTs, limiting the generalizability of the results to a wider population. The scope of this review does not include oxidative stress, but this remains a useful future area of investigation.

In conclusion, this review has found evidence suggesting that SGLT2 inhibitors improve adipokine profiles and insulin sensitivity, but the analysis shows little evidence of improvement in other inflammatory biomarkers including CRP. Adipokines are important aetiological factors in CVD and thus may be a contributing factor to the cardiovascular-protective effects of SGLT2 inhibitors.

AUTHOR CONTRIBUTIONS

Leonardo Buttice was responsible for writing the initial manuscript, screening, data collection, analysis, and the final review. Jonathan J. H. Bray supervised the project, and was responsible for the design, conceptualization, writing of the methods and reviewing the final manuscript. Maryam Ghani was responsible for data collection and the quality and risk-of-bias analysis, and contributed to the writing of the introduction. Janahan Suthakar was responsible for screening and data collection. Sathyan Gnanalingham was responsible for screening. Elliott Carande, Brett W. C. Kennedy, Alex Pitcher, James H. P. Gamble, Mahmood Ahmad, Andrew Lewis, Peter Jüni, Jeffrey W. Stephens and Oliver J. Rider were responsible for reviewing the draft of the final manuscript.

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None declared.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data is available at request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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